

Appendix 2

Clean copy of amended claims 21, 23, 27, 29, 31, 33-40, 98,
and 100-106 (37 C.F.R. §1.121(c)(i)).

D¹ ~~6~~ 21. (Once amended) The method of claim ~~102~~, which is for
improving naturally-occurring vision in an animal, in the absence
of any ophthalmologic disorder, disease, or injury.

D² ~~7~~ 23. (Once amended) The method of claim ~~102~~, wherein the
compound is administered to said animal in combination with an
effective amount of one or more factor(s) useful in treating vision
disorders, improving vision, treating memory impairment, or
enhancing memory performance in an animal.

D³ ~~9~~ 27. (Once amended) The method of claim ~~102~~, wherein the
nerve-related vision disorder is retinal ischemia.

D⁴ ~~11~~ 29. (Once amended) The method of claim ~~102~~, wherein the
nerve-related vision disorder is optic nerve transection.

D⁵ ~~13~~ 31. (Once amended) The method of claim ~~102~~, wherein the
nerve-related vision disorder is diabetes.

15~~33~~. (Once amended) The method of claim ~~102~~¹, wherein the nerve-related vision disorder is macular degeneration.

16~~34~~. (Once amended) The method of claim ~~102~~¹, wherein the nerve-related vision disorder is glaucoma related degeneration.

17~~35~~. (Once amended) The method of claim ~~102~~¹, wherein the nerve-related vision disorder is cataract related degeneration.

18~~36~~. (Once amended) The method of claim ~~102~~¹, wherein the nerve-related vision disorder is a detached retina.

19~~37~~. (Once amended) The method of claim ~~102~~¹, wherein the nerve-related vision disorder is inflammation related degeneration.

20~~38~~. (Once amended) The method of claim ~~102~~¹, wherein the nerve-related vision disorder is photoreceptor degeneration.

21~~39~~. (Once amended) The method of claim ~~102~~¹, wherein the nerve-related vision disorder is optic neuritis.

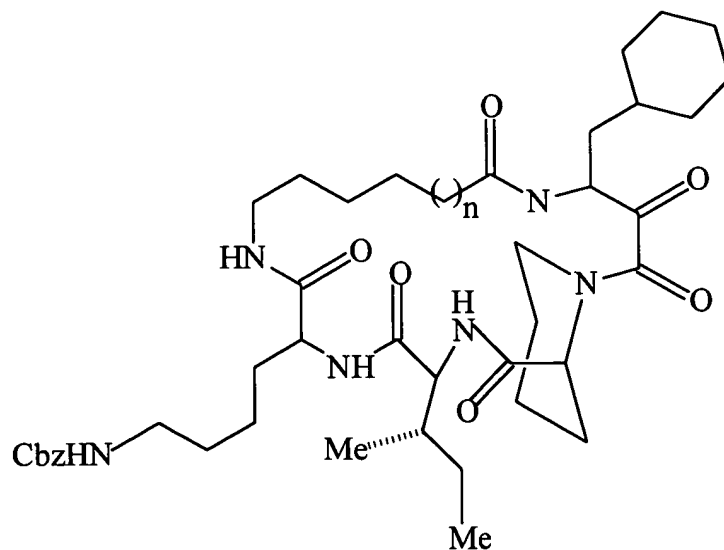
22~~40~~. (Once amended) The method of claim ~~102~~¹, wherein the nerve-related vision disorder is dry eye degeneration.

107 ~~23~~ 98. (Once amended) The method of claim ~~102~~, wherein the compound has an affinity for an FKBP-type immunophilin.

~~25~~ 100. (Once amended) The method of claim ~~102~~, wherein the compound is immunosuppressive.

~~26~~ 101. (Once amended) The method of claim ~~102~~, wherein the compound is non-immunosuppressive.

108
~~1~~ 102. (Once amended) A method for treating a nerve-related vision disorder, improving vision, treating memory impairment, or enhancing memory performance in an animal, which comprises administering to said animal an effective amount of a compound selected from the group consisting of:



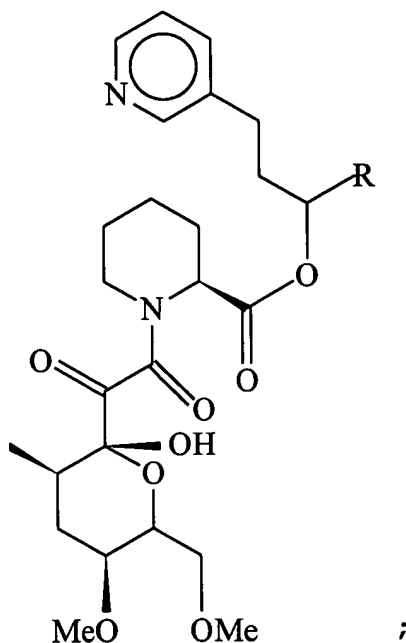
wherein n is 1; 2; or 3;

4-(4-methoxyphenyl)butyl (2S)-1-[2-(3,4,5-trimethoxyphenyl)acetyl]hexahydro-2-pyridinecarboxylate;

4-(4-methoxyphenyl)butyl (2S)-1-[2-(3,4,5-trimethoxyphenyl)acryloyl]hexahydro-2-pyridinecarboxylate;

4-(4-methoxyphenyl)butyl (2S)-1-[2-(3,4,5-trimethoxyphenyl)propanoyl]hexahydro-2-pyridinecarboxylate;

4-(4-methoxyphenyl)butyl (2S)-1-[2-oxo-2-(3,4,5-trimethoxyphenyl)acetyl]hexahydro-2-pyridinecarboxylate;



3-cyclohexylpropyl (2S)-1-(3,3-dimethyl-2-oxopentanoyl)hexahydro-2-pyridinecarboxylate;

3-phenylpropyl (2S)-1-(3,3-dimethyl-2-oxopentanoyl)hexahydro-2-pyridinecarboxylate;

3-(3,4,5-trimethoxyphenyl)propyl (2S)-1-(3,3-dimethyl-2-oxopentanoyl)hexahydro-2-pyridinecarboxylate;

(1R)-2,2-dimethyl-1-phenethyl-3-butenyl (2S)-1-(3,3-dimethyl-2-oxopentanoyl)hexahydro-2-pyridinecarboxylate;

(1R)-1,3-diphenylpropyl (2S)-1-(3,3-dimethyl-2-oxopentanoyl)hexahydro-2-pyridinecarboxylate;

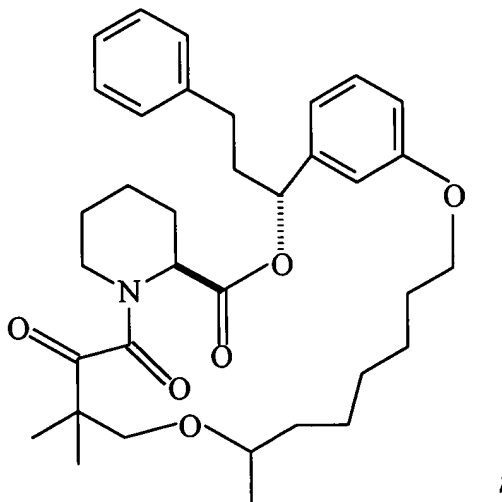
(1R)-1-cyclohexyl-3-phenylpropyl (2S)-1-(3,3-dimethyl-2-oxopentanoyl)hexahydro-2-pyridinecarboxylate;

(1S)-1,3-diphenylpropyl (2S)-1-(3,3-dimethyl-2-oxopentanoyl)hexahydro-2-pyridinecarboxylate;

(1S)-1-cyclohexyl-3-phenylpropyl (2S)-1-(3,3-dimethyl-2-oxopentanoyl)hexahydro-2-pyridinecarboxylate;

D⁸ cont
(22aS)-15,15-dimethylperhydropyrido[2,1-c][1,9,4]dioxazacyclononadecine-1,12,16,17-tetraone;

(24aS)-17,17-dimethylperhydropyrido[2,1-c][1,9,4]dioxazacyclohenicosine-1,14,18,19-tetraone;

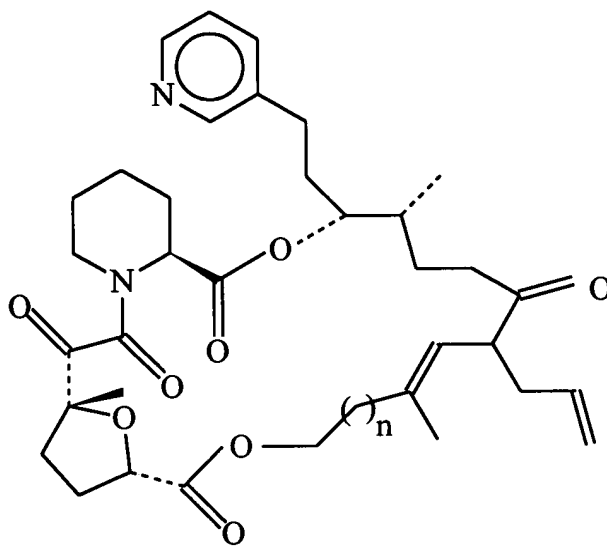


(3R,4R,23aS)-8-allyl-4,10-dimethyl-3-[2-(3-pyridyl)ethyl]-1,3,4,5,6,7,8,11,12,15,16,17,18,20,21,22,23,23a-octadecahydro-14H-

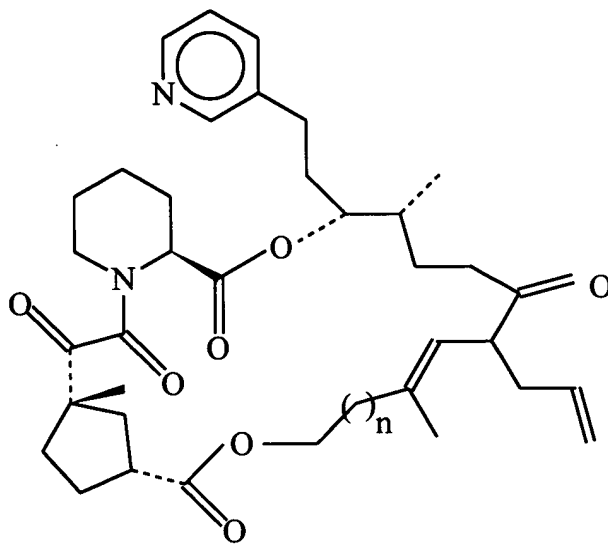
pyrido[2,1-c][1,10,4]dioxazacycloicosine-1,7,14,17,18-pentaone;

(3R,4R,24aS)-8-allyl-4,10-dimethyl-3-[2-(3-pyridyl)ethyl]-
1,3,4,5,6,7,8,11,12,14,15,16,17,18,19,21,22,23, 24,24a-
icosahydropyrido[2,1-c] [1,11,4]dioxazacyclohenicosine-
1,7,14,18,19-pentaone;

(3R,4R,25aS)-8-allyl-4,10-dimethyl-3-[2-(3-pyridyl)ethyl]-
1,3,4,5,6,7,8,11,12,15,16,17,18,19,20,22,23, 24,25,25a-icosahydro-
14H-pyrido[2,1-c] [1,12,4]dioxazacyclodocosine-1,7,14,19,20-
pentaone;



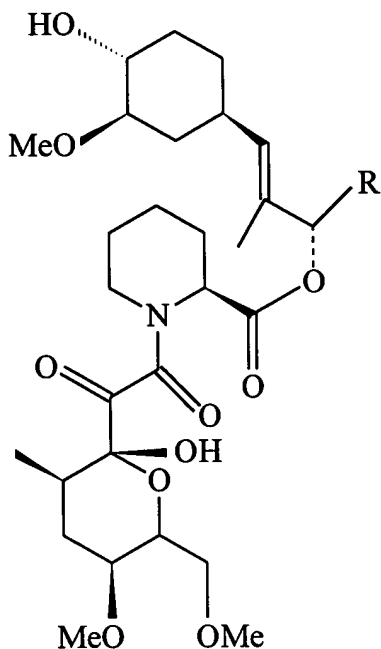
wherein n is 1; 2; or 3;



wherein n is 1; 2; or 3;

T,1380

W⁸ cont.

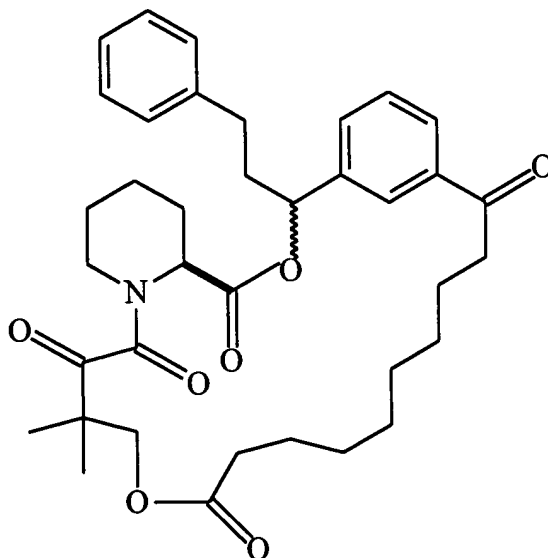


(1R)-1-(3-benzoylphenyl)-3-phenylpropyl (1R)-2-(3,3-dimethyl-2-oxopentanoyl)cyclohexane-1-carboxylate;

(1R)-1-[3-(diallylcarbamoyl)phenyl]-3-phenylpropyl;

(1R)-2-(3,3-dimethyl-2-oxopentanoyl)cyclohexane-1-carboxylate;

T,1381



ethyl 1-(2-oxo-3-phenylpropanoyl)-2-piperidinecarboxylate;

138

D

ethyl 1-pyruvoyl-2-piperidinecarboxylate;
ethyl 1-(2-oxobutanoyl)-2-piperidinecarboxylate;
ethyl 1-(3-methyl-2-oxobutanoyl)-2-piperidinecarboxylate;
ethyl 1-(4-methyl-2-oxopentanoyl)-2-piperidinecarboxylate;
ethyl 1-(3,3-dimethyl-2-oxobutanoyl)-2-piperidinecarboxylate;
ethyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate;
4-[2-(ethyloxycarbonyl)piperidino]-2,2-dimethyl-3,4-dioxobutyl
acetate;
ethyl 1-[2-(2-hydroxytetrahydro-2H-2-pyranyl)-2-oxoacetyl]-2-
piperidinecarboxylate;
ethyl 1-[2-(2-methoxytetrahydro-2H-2-pyranyl)-2-oxoacetyl]-2-
piperidinecarboxylate;
ethyl 1-[2-(1-hydroxycyclohexyl)-2-oxoacetyl]-2-
piperidinecarboxylate;
ethyl 1-[2-(1-methoxycyclohexyl)-2-oxoacetyl]-2-
piperidinecarboxylate;
ethyl 1-(2-cyclohexyl-2-oxoacetyl)-2-piperidinecarboxylate;
ethyl 1-(2-oxo-2-piperidinoacetyl)-2-piperidinecarboxylate;
ethyl 1-[2-(3,4-dihydro-2H-6-pyranyl)-2-oxoacetyl]-2-
piperidinecarboxylate;
ethyl 1-(2-oxo-2-phenylacetyl)-2-piperidinecarboxylate;
ethyl 1-(4-methyl-2-oxo-1-thioxopentyl)-2-piperidinecarboxylate;
3-phenylpropyl 1-(2-hydroxy-3,3-dimethylpentanoyl)-2-
piperidinecarboxylate;

(1R)-1-phenyl-3-(3,4,5-trimethoxyphenyl)propyl 1-(3,3-dimethylbutanoyl)-2-piperidinecarboxylate;

(1R)-1,3-diphenylpropyl 1-(benzylsulfonyl)-2-piperidinecarboxylate;
3-(3,4,5-trimethoxyphenyl)propyl 1-(benzylsulfonyl)-2-piperidinecarboxylate;

1-(2-[(2R,3R,6S)-6-[(2S,3E,5E,7E,9S,11R)-2,13-dimethoxy-3,9,11-trimethyl-12-oxo-3,5,7-tridecatrienyl]-2-hydroxy-3-methyltetrahydro-2H-2-pyranyl)-2-oxoacetyl)-2-piperidinecarboxylic acid;

108 cont
methyl 1-(2-[(2R,3R,6S)-6-[(2S,3E,5E,7E,9S,11R)-2,13-dimethoxy-3,9,11-trimethyl-12-oxo-3,5,7-tridecatrienyl]-2-hydroxy-3-methyltetrahydro-2H-2-pyranyl)-2-oxoacetyl)-2-piperidinecarboxylate;

isopropyl 1-(2-[(2R,3R,6S)-6-[(2S,3E,5E,7E,9S,11R)-2,13-dimethoxy-3,9,11-trimethyl-12-oxo-3,5,7-tridecatrienyl]-2-hydroxy-3-methyltetrahydro-2H-2-pyranyl)-2-oxoacetyl)-2-piperidinecarboxylate;

benzyl 1-(2-[(2R,3R,6S)-6-[(2S,3E,5E,7E,9S,11R)-2,13-dimethoxy-3,9,11-trimethyl-12-oxo-3,5,7-tridecatrienyl]-2-hydroxy-3-methyltetrahydro-2H-2-pyranyl)-2-oxoacetyl)-2-piperidinecarboxylate;

1-phenylethyl 1-(2-[(2R,3R,6S)-6-[(2S,3E,5E,7E,9S,11R)-2,13-dimethoxy-3,9,11-trimethyl-12-oxo-3,5,7-tridecatrienyl]-2-hydroxy-3-methyltetrahydro-2H-2-pyranyl)-2-oxoacetyl)-2-

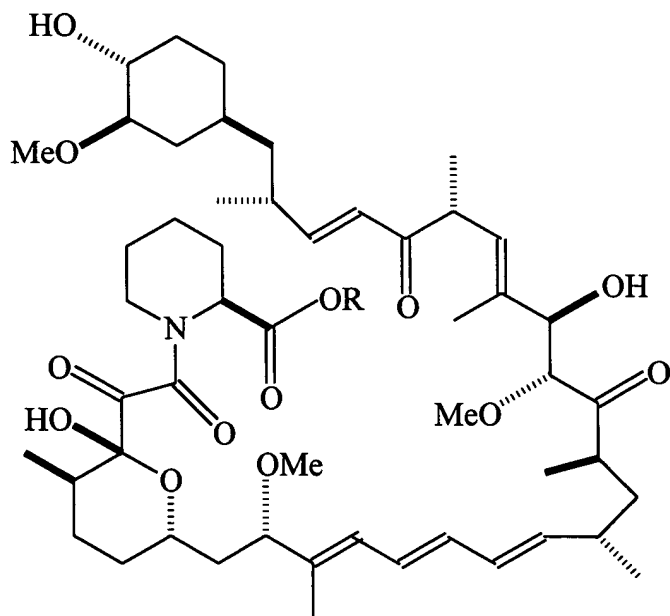
piperidinecarboxylate;

(Z)-3-phenyl-2-propenyl 1-(2-[(2R,3R,6S)-6-[(2S,3E,5E,7E,9S,11R)-2,13-dimethoxy-3,9,11-trimethyl-12-oxo-3,5,7-tridecatrienyl]-2-hydroxy-3-methyltetrahydro-2H-2-pyranyl)-2-oxoacetyl)-2-piperidinecarboxylate;

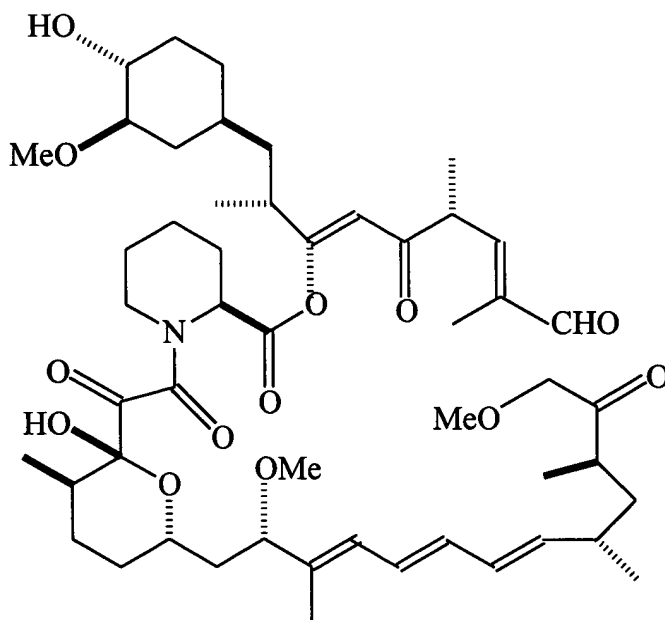
3-(3,4-dimethoxyphenyl)propyl 1-(2-[(2R,3R,6S)-6-[(2S,3E,5E,7E,9S,11R)-2,13-dimethoxy-3,9,11-trimethyl-12-oxo-3,5,7-tridecatrienyl]-2-hydroxy-3-methyltetrahydro-2H-2-pyranyl)-2-oxoacetyl)-2-piperidinecarboxylate;

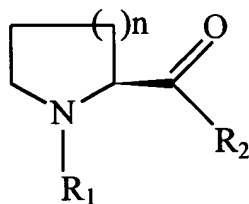
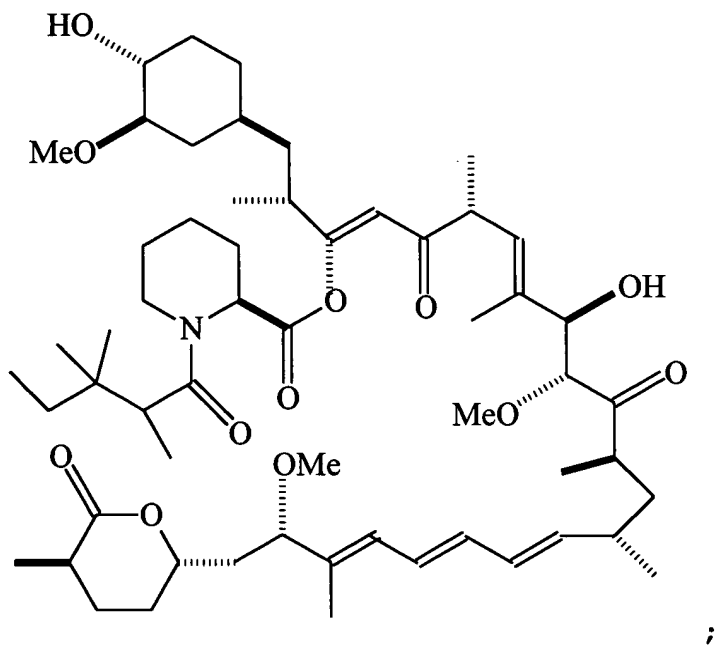
208 cont
N2-benzyl-1-(2-[(2R,3R,6S)-6-[(2S,3E,5E,7E,9S,11R)-2,13-dimethoxy-3,9,11-trimethyl-12-oxo-3,5,7-tridecatrienyl]-2-hydroxy-3-methyltetrahydro-2H-2-pyranyl)-2-oxoacetyl)-2-piperidinecarboxylate;

N2-(3-phenylpropyl)-1-(2-[(2R,3R,6S)-6-[(2S,3E,5E,7E,9S,11R)-2,13-dimethoxy-3,9,11-trimethyl-12-oxo-3,5,7-tridecatrienyl]-2-hydroxy-3-methyltetrahydro-2H-2-pyranyl)-2-oxoacetyl)-2-piperidinecarboxylate;



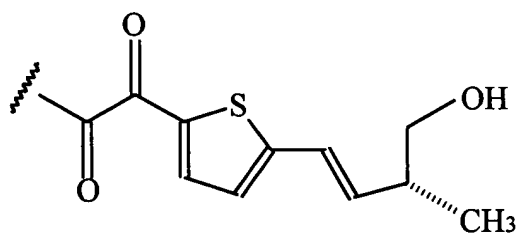
wherein R is methyl (Me); or benzyl (Bn);



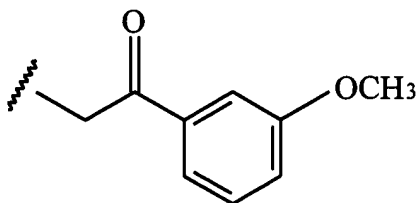


wherein $n = 2$,

$R_1 =$

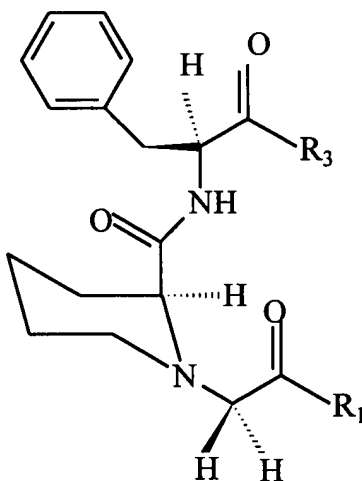


or



and

$R_2 = \text{Phe-o-tert-butyl};$



wherein

$R_1 = m\text{-OCH}_3\text{Ph},$

$R_3 = \text{Val-o-tert-butyl};$

$R_1 = m\text{-OCH}_3\text{Ph},$

$R_3 = \text{Leu-o-tert-butyl};$

$R_1 = m\text{-OCH}_3\text{Ph},$

$R_3 = \text{Ileu-o-tert-butyl};$

$R_1 = m\text{-OCH}_3\text{Ph},$

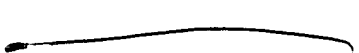
$R_3 = \text{hexahydro-Phe-o-tert-butyl};$

$R_1 = m\text{-OCH}_3\text{Ph},$

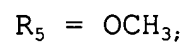
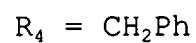
$R_3 = \text{allylalanine-o-tert-butyl};$

$R_1 = \text{B-naphthyl},$

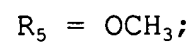
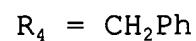
$R_3 = \text{Val-o-tert-butyl};$



P8 cont



or



wherein

$R_1 = m\text{-OCH}_3\text{Ph}$

$X = \text{trans-CH=CH}$

$R_4 = \text{H}$

$Y = \text{OC(o)Ph};$

$R_1 = \text{OCH}_3\text{Ph}$

$X = \text{trans-CH=CH}$

$R_4 = \text{H}$

$Y = \text{OC(o)CF}_3;$

$R_1 = m\text{-OCH}_3\text{Ph}$

$X = \text{trans-CH=CHI}$

$R_4 = -$

$Y = -;$

$R_1 = m\text{-OCH}_3\text{Ph}$

$X = \text{trans-CH=CH}$

$R_4 = \text{H}$

$Y = \text{OCH}_2\text{CH=CH}_2;$

$R_1 = m\text{-OCH}_3\text{Ph}$

$X = \text{C=O}$

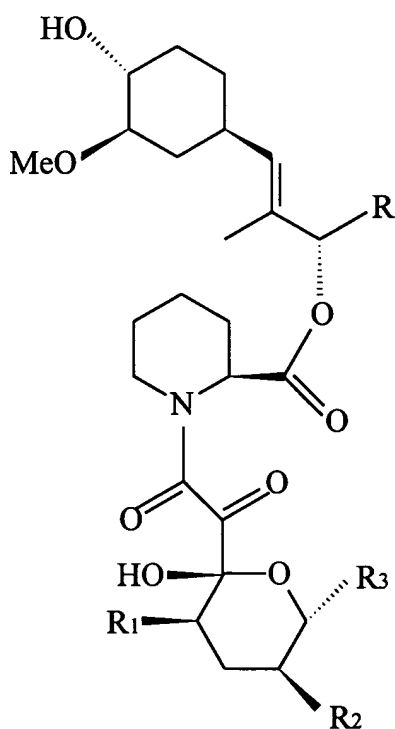
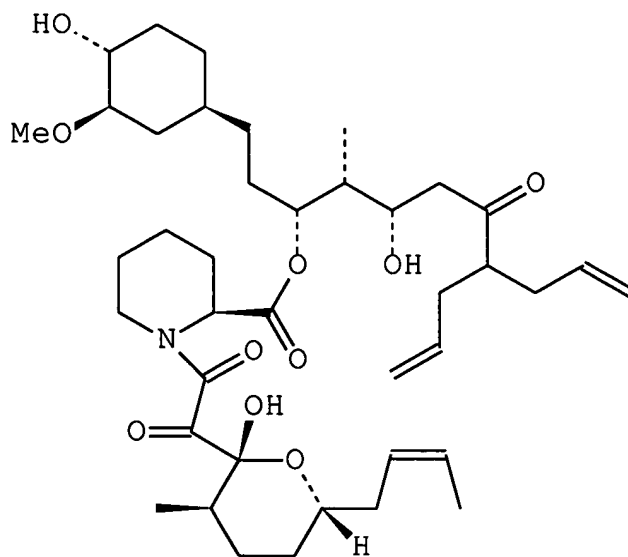
$R_4 = \text{H}$

146

D

108 cont

Y = Ph;



wherein

7,1480
R₁ = H, R₂ = OMe, and R₃ = CH₂OMe;

R₁ = H, R₂ = H, and R₃ = H;

R₁ = Me, R₂ = H, and R₃ = H;

(E)-3-(3,4-dichlorophenyl)-2-propenyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate;

(E)-3-(3,4,5-trimethoxyphenyl)-2-propenyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate;

(E)-3-phenyl-2-propenyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate;

108 cont
(E)-3-((3-(2,5-dimethoxy)-phenylpropyl)phenyl)-2-propenyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate;

4-(4-methoxyphenyl)butyl 1-(2-oxo-2-phenylacetyl)-2-piperidinecarboxylate;

3-phenylpropyl 1-(2-oxo-2-phenylacetyl)-2-piperidinecarboxylate;

3-(3-pyridyl)propyl 1-(2-oxo-2-phenylacetyl)-2-piperidinecarboxylate;

3-(3-pyridyl)propyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate;

4-phenyl-1-(3-phenylpropyl)butyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate;

4-(4-methoxyphenyl)butyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate;

1-(4-methoxyphenethyl)-4-phenylbutyl 1-(3,3-dimethyl-2-

oxopentanoyl)-2-piperidinecarboxylate;

3-(2,5-dimethoxyphenyl)propyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate;

3-(1,3-benzodioxol-5-yl)propyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate;

1-phenethyl-3-phenylpropyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarboxylate;

4-(4-methoxyphenyl)butyl 1-(2-cyclohexyl-2-oxoacetyl)-2-piperidinecarboxylate;

3-cyclohexylpropyl 1-(2-cyclohexyl-2-oxoacetyl)-2-piperidinecarboxylate;

3-phenylpropyl 1-(2-cyclohexyl-2-oxoacetyl)-2-piperidinecarboxylate;

3-cyclohexylpropyl 1-(3,3-dimethyl-2-oxobutanoyl)-2-piperidinecarboxylate;

3-phenylpropyl 1-(3,3-dimethyl-2-oxobutanoyl)-2-piperidinecarboxylate;

4-(4-methoxyphenyl)butyl 1-(3,3-dimethyl-2-oxobutanoyl)-2-piperidinecarboxylate;

4-phenyl-1-(3-phenylpropyl)butyl 1-(3,3-dimethyl-2-oxobutanoyl)-2-piperidinecarboxylate;

Way-124,666;

rapamycin;

Rap-Pa; and

149

D

SLB-506,

or a pharmaceutically acceptable salt, ester, or solvate thereof,

wherein the nerve-related vision disorder is selected from the group consisting of visual impairments; orbital disorders; disorders of the lacrimal apparatus; disorders of the eyelids; disorders of the conjunctiva; disorders of the cornea; cataract; disorders of the uveal tract; disorders of the retina; disorders of the optic nerve or visual pathways; free radical induced eye disorders and diseases; immunologically-mediated eye disorders and diseases; eye injuries; and symptoms and complications of eye disease, eye disorder, and eye injury.

D8 cont
~~2~~ 103. (Once amended) The method of claim ~~102~~¹, wherein the compound is Way-124,666.

~~3~~ 104. (Once amended) The method of claim ~~102~~¹, wherein the compound is rapamycin.

~~4~~ 105. (Once amended) The method of claim ~~102~~¹, wherein the compound is Rap-Pa.

~~5~~ 106. (Once amended) The method of claim ~~102~~¹, wherein the compound is SLB-506.

Table E

Efficacy of representative compounds from different immunophilin ligand series in protecting retinal ganglion cell axons from degeneration following optic nerve transection

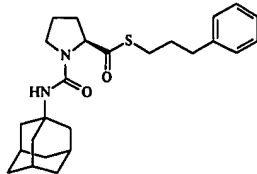
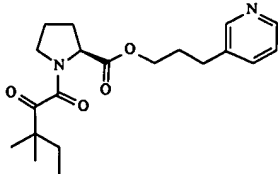
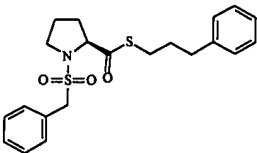
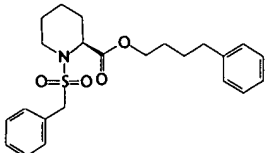
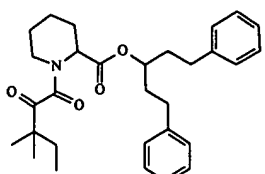
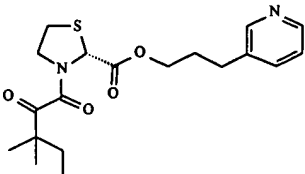
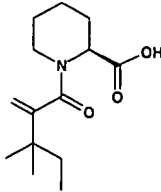
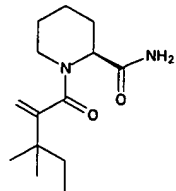
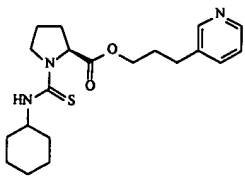
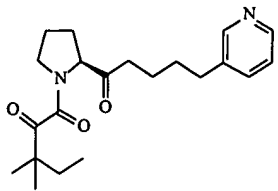
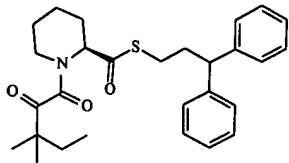
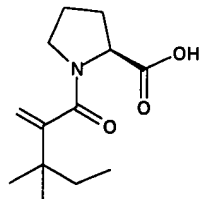
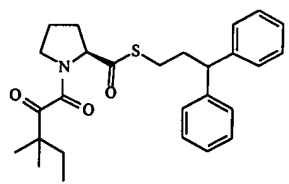
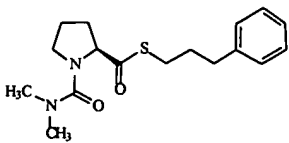
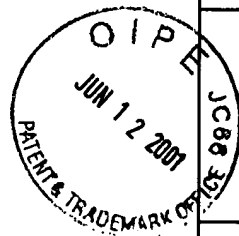
Compound	Structure	Comments	RT97+RGC axon density 14 days after ON transection (% ON axons rescued)
B		Adamantyl Thioester of urea K_i Rotamase=149 nM Clearance=? μ l/min.	100.0% \pm 5.2% SEM
A GPI 1046		Ester K_i rotamase=7.5 nM Clearance=63.8 μ l/min.	60.5% \pm 3.9 SEM
C		Sulfonamide K_i rotamase=107 nM Clearance=31.1 μ l/min.	60.4% \pm 3.1% SEM
D		Pipecolic sulfonamide K_i rotamase= nM Clearance= μ l/min.	58.4% \pm 6.4% SEM
E		Ester of pipecolic acid K_i rotamase=20 nM Clearance=41.8 μ l/min.	56.6% \pm 9.4% SEM
F		Proline heterocycle Analog of GPI 1046 K_i rotamase=272 nM Clearance=? μ l/min	55.1% \pm 5.9% SEM
G		Pipecolic acid dimethyl ketone K_i rotamase>10,000 nM Clearance=? μ l/min.	34.0% \pm 4.8% SEM

Table E continued

Compound	Structure	Comments	RT97+RGC axon density 14 days after ON transection (% ON axons rescued)
H		Ki rotamase= nM Clearance=? $\mu\text{l/min.}$	30.3% $\pm 8.0\%$ SEM
I		Ester of Thiourea Ki rotamase=131 nM Clearance=8.0 $\mu\text{l/min.}$	23.8% ± 5.3 SEM
J		Ketone analog of GPI 1046 Ki rotamase=210 nM Clearance=1.5 $\mu\text{l/min.}$	15.8% $\pm 4.8\%$ SEM
K		Pipecolic acid Thioester Ki rotamase=86 nM Clearance=4.5 $\mu\text{l/min.}$	13.0% $\pm 4.2\%$ SEM
L		Prolyl acid Ki rotamase= >7743 nM Clearance=5.2 $\mu\text{l/min.}$	7.8% $\pm 3.0\%$ SEM
M		Thioester Ki rotamase=7 nM Clearance=12.5 $\mu\text{l/min.}$	-6.3% $+3.9\%$ SEM
N		Ki rotamase=722 nM Clearance=21.9 $\mu\text{l/min.}$	

152

D



D9 cont